

### REMARKS

Claims 2-67 will be pending in the application upon entry of the present amendment, claim 1 having been cancelled and new claims 41-67 added. Claims 2-11, 27, and 41-67 are under examination, claims 12-26 and 28-40 being withdrawn from consideration as drawn to a non-elected invention. The claims in the present amendment are identical to those in the claim amendment filed in the Reply to Office Action filed on June 27, 2003. The present amendment reiterates the claims provided in the Reply and places them in conformity with the revised amendment practice. Specifically, the text of the cancelled claim (i.e., claim 1) has been removed, and the status and text of the withdrawn claims (i.e., claims 12-26 and 28-40) have been added.

Support for the new claims, which are drawn to the same invention as elected Group I, is provided throughout the specification. For example, support for new claims 41-67 is found in Example 2 (page 52, line 9, to page 53, line 6) and at page 5, lines 23 to 30. Additional support is discussed below. No new matter has been added.

### Objections

The Examiner objected to the abstract. Applicants have amended the abstract to address the objection.

The specification is objected to for lacking a "Brief Description of the Drawings." Applicants respectfully point out that a Brief Description of the Drawings is present in the application as filed, beginning at page 48, line 26 of the application.

Applicants therefore request withdrawal of the objections to the present application.

### 35 U.S.C. § 112, second paragraph

Claim 5-8 are rejected as being indefinite for lack of antecedent basis for the term "the peptide" in claim 1. These claims have been amended to correct this by replacing "the" with "a."

Claim 9 is rejected for lack of antecedent basis for the term "the secondary antibody." Claim 9 has been amended to depend from claim 7, which provides proper antecedent basis for the term.

Claims 10 and 11 have been rejected for use of the term "...with, as an index..." Claim 11 depends from claim 10. Claim 10 has been amended to recite "...binding is detected as a change in the expression level..." thus addressing the rejection of both claims 10 and 11.

In view of the claim amendments discussed above, applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 112, first paragraph

*Enablement*

Claims 1-11 and 27 are rejected for alleged lack of enablement related to scope. Claim 1 has been cancelled, replaced with new claim 41. To the extent that the rejection may apply to the claims as amended, applicants respectfully traverse.

The Examiner states

[t]he specification is enabling for a method of screening for compounds that inhibit the binding of the TAK1 set forth by SEQ ID NO:2 with the TAB1 set forth by SEQ ID NO:4. However, the specification does not reasonably provide enablement for methods of screening for compounds that inhibit the binding of any TAK1 with any TAB1 (Office Action at page 3).

The Office Action also states that the scope of the claims is not supported by the specification

because the specification does not establish: (A) which TAB1 and TAK1 proteins are to be used in the binding assays; (B) regions of the TAK1 set forth by SEQ ID NO:2 and the TAB1 set forth by SEQ ID NO:4 which may be modified without effecting the binding activity; (C) the general tolerance of the binding activity to modification of the TAK1 set forth by SEQ ID NO:2 and the TAB1 set forth by SEQ ID NO:4 and the extent of such tolerance; (D) a rational and predictable scheme for modifying any residues within the TAK1 set forth by SEQ ID NO:2 and the TAB1 set forth by SEQ ID NO:4 with an expectation of obtaining the desired

biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices of variant TAK1 and TAB1 proteins is likely to be successful. (Office Action at the paragraph bridging pages 4-5)

New independent claims 41, 61, 63, or 67 narrowly define the structures of the TAK1 and TAB1 proteins used in the claimed methods. One specified category of TAK1 protein comprises amino acids 76 to 303 of SEQ ID NO:2. Such proteins are described at page 7, lines 10 to 17. A second category of TAK1 can bind TAB1 and comprises amino acids 76 to 303 of SEQ ID NO:2, with one or more (up to 20) amino acid substitutions, deletions, and/or additions to that sequence. The specification describes such molecules at, for example, page 7, lines 25 to 29, and at page 8, line 13, to page 9, line 1. A third category of TAK1 specified in claims 41, 61, 63, or 67 is a polypeptide that is encoded by a DNA that hybridizes to the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulphate, and 50% formamide. The specification discusses such a TAK1 at page 12, line 35, to page 14, line 24.

Claims 41, 61, 63, and 67 also specify that the TAB1 protein either comprise amino acids 437 to 504 of SEQ ID NO:4 (specification at page 11, lines 7 to 9); bind a TAK1 and comprise amino acids 437 to 504 of SEQ ID NO:4, with one or more (up to 20) amino acid substitutions, deletions, and/or additions (specification at page 11, lines 16-20); or be encoded by a DNA sequence that hybridizes to the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulphate, and 50% formamide (specification at page 12, line 35, to page 13, line 24).

Furthermore, applicants have provided at least two working examples of TAK1 proteins that bind to a TAB1. Example 1 of the specification discloses a TAK1 partial peptide (amino acids 77-303 of SEQ ID NO:2) fused with a GAL4 DNA binding domain, as well as a full-length TAK1 (SEQ ID NO:2) fused with a GAL4 DNA binding domain.

In addition, Reference Example 1 of the specification (page 54, line 1) discloses a TAB1 fusion protein that includes the C-terminal 68 amino acid residues of TAB1 fused with the transcription activation domain of VP16. Other specific examples of TAB1 proteins are

provided in the specification at page 8, line 29, to page 9, line 2 and page 9, lines 10 to 35. Additional information regarding TAB1 proteins is set forth in the specification at page 11, line 7, to page 12, line 9.

As described above, applicants believe that the claims now adequately specify TAB1 and TAK1 molecules. The claims also specify that the TAK1 proteins of (ii) and (iii) bind the TAB1 and that the TAB1 proteins of (v) and (vi) bind the TAK1, therefore ensuring that the proteins used in the claimed method possess the necessary functionality. The specification provides ample description of appropriate binding assays, for example at page 20, line 9 to page 31, line 15. Given the teachings in the specification concerning the binding regions of both proteins and assays useful for detecting binding, clearly one of skill in the art would be able to make and use TAB1 and TAK1 proteins across the full scope of the claims. Assay of the TAB1 and TAK1 proteins for binding activity does not rise to the level of undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) made it clear that screening for activity to find species that fall within a claim is not undue experimentation where the techniques required for such screening are routine, as in the present case. The making and using of the claimed polypeptides would employ techniques that are disclosed in the specification and that are routine in the art.

Regarding predictability (see item (D) in the quotation from the Office Action), the prior art generally teaches that "proteins are surprisingly tolerant of amino acid substitutions" (see page 1306, second column, first full paragraph of Bowie et al., 1990, "Deciphering the message in protein sequences: tolerance to amino acid substitutions," *Science* 247:1306-1310, copy attached). Based on the teachings of Bowie et al., one would expect to find that over half (and possibly well over half) of random substitutions in any given protein would result in a protein with full or nearly full activity. This concept is also addressed in the specification at page 9, lines 2 to 9, which states

[I]t has been already known that a peptide having an amino acid sequence that is modified by one or more amino acid substitutions, deletions, and/or additions in a amino acid sequence is still capable of having its original biological activity (Mark, D. F. et al., *Proc. Natl. Acad. Sci. USA* (1984) 81, 5662-5666; Zoller, M. J. &

Smith, M. Nucleic Acids Research (1982) 10, 6487-6500;  
Wang, A. et al., Science 224, 1431-1433; Dalbadie-McFarland, G.  
et al., Proc. Natl. Acad. Sci USA (1982) 79, 6409-6413).

In view of the above discussion, applicants respectfully request withdrawal of the rejection for lack of enablement.

*Written description*

Claims 1-11 and 27 have also been rejected for lack of written description. The Examiner states

[t]he specification teaches the structure of only a single TAK1 molecule and a single TAB1 molecule which, are representative species of such genera. Moreover, the specification fails to describe any other representative species of TAK1 and TAB1 by identifying characteristics or properties other than the functionality of binding with each other. (Office Action at the paragraph bridging pages 5 and 6)

While disagreeing that claims 1-11 and 27 as originally filed failed to meet the written description requirement, applicants have amended the independent claims to provide more explicit descriptions of both structure and function of the TAK1 and TAB1 utilized in the claimed methods.

The Written Description Guidelines state that the written description requirement can be satisfied by:

sufficient description of a representative number of species by actual reduction to practice...or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (Federal Register, Vol. 66, No. 4, at page 1104).

Each TAK1 that can be utilized must fall within one of three categories (i), (ii), or (iii) in claim 41, 61, and 67, or corresponding categories (1), (2), or (3) in claim 63, which clearly meets

the written description requirement under U.S. law. Category (i) TAK1 contains a specified sequence, so is plainly supported by the description of that sequence, e.g., at page 7, lines 13 to 17. Category (ii) TAK1 is similar but allows 1-20 amino acids to be substituted, deleted, and/or added (specification at page 8, lines 13 to 22). This type of language is even more precise than the "percent homology" language explicitly permitted in Example 16 of the Synopsis of Application Written Description Guidelines (the "Synopsis"), particularly as it is coupled in Category (ii) with a limitation regarding the activity of the protein. Category (iii) TAK1 is written in terms of hybridization to a specified probe, coupled with a limitation requiring that the protein display the necessary binding activity (specification at page 13, lines 15 to 24). Example 9 of the Synopsis states that a sequence described in terms of hybridization meets the written description requirement, a position validated by the Federal Circuit in *Enzo Biochem. Inc. v Genprobe Inc.*, 296 F3d 1316 (Fed. Cir. 2002). The same rationale applies to the written description provided for TAB1 as presently limited in the independent claims (e.g., in categories (iv)-(vi) of claims 41, 61, and 67, and corresponding categories (4), (5), and (6) of claim 63.

The specification also teaches specific examples of TAK1 and TAB1 proteins. Examples of TAK1 proteins include full-length SEQ ID NO:2 (page 7, lines 4 to 6); amino acids 76 to 303 of SEQ ID NO:2 (page 7, lines 8 to 17); and a mouse-derived TAK1 in which Ser is substituted for Gly at amino acid 16, Arg is substituted for His at amino acid 372, Val is substituted for Ala at amino acid 400, Ala is substituted for Thr at amino acid 403, and Ala is substituted for Thr at amino acid 449 (page 8, line 31 to page 9, line 1).

Examples of TAB1 proteins include a TAB1 fusion protein that binds TAK1 and includes the C-terminal 68 amino acid residues of TAB1 fused with the transcription activation domain of VP16 (Reference Example 1 of the specification at page 54, line 1). The specification also teaches a TAB1 that includes a complete TAB1 as shown in SEQ ID NO:4 (page 10, lines 14 to 16), TAB1 with amino acids 437-504 of SEQ ID NO:4 (page 11, lines 7 to 9), and SEQ ID NO:4 in which Arg is substituted for Ser at amino acid 52 (page 11, lines 21 to 25). Additional information regarding TAB1 proteins is provided in the specification at page 11, line 7, to page 12, line 9.

Finally, applicants remind the Examiner that the present claims are drawn to methods, not compositions of matter. Courts have never required that all reagents specified in a method claim be described at the same level of specificity as the compositions claimed in a composition of matter claim. Accordingly, applicants request withdrawal of the rejection related to lack of written description.

In view of the foregoing, applicants believe that the claims meet the requirements for written description and enablement and request withdrawal of the rejections under 35 U.S.C. § 112, paragraph 1.

35 U.S.C. § 102 (b)

Claim 1 has been rejected for anticipation in view of Matsuomoto et al. (1998). According to the Examiner, Matsuomoto et al. teach a method of screening for the ability of inhibitors of TGF- $\beta$  signaling to inhibit TAK1/TAB1 interaction. Claim 1 has been cancelled. To the extent that the rejection applies to the newly added independent claims, it is traversed.

To anticipate a claim, a reference must teach every element of the claim. The present claims are drawn to methods of identifying a protein that inhibits TAK1/TAB1 binding and inhibits expression of an inflammatory cytokine (claims 41 and 63) or inhibits inflammation (claim 63) or is identified as an inhibitor of an inflammatory cytokine (claims 61 and 67). Matsuomoto et al. discloses that TAB1 activates TAK1 by binding TAK1 and that TAB1 is downstream of TGF- $\beta$  in the TGF- $\beta$  signaling pathway. TGF- $\beta$  is not a pro-inflammatory cytokine. In fact, TGF- $\beta$  is associated with anti-inflammatory properties, as shown in Kulkarni et al. (1993, "Transforming growth factor  $\beta_1$  null mutation in mice causes excessive inflammatory response and early death," Proc. Nat. Acad. Sci. USA 90:770-774; copy enclosed). Matsuomoto et al. does not provide evidence of any relationship between TAK1/TAB1 binding and expression of inflammatory cytokines or inflammation.

Claim 41 is drawn to a method of screening for a compound that both inhibits TAK1/TAB1 binding and inhibits expression of an inflammatory cytokine. Matsumoto does not teach such a method.

Claim 61 is drawn to a screening method in which a compound that is an inhibitor of inflammatory cytokine activity is selected and the compound is tested for the ability to inhibit TAK1/TAB1 binding. Matsuomoto et al. does not teach such a method.

Claim 63 is drawn to a screening method in which a compound that inhibits TAK1/TAB1 binding is selected and tested for its ability to inhibit inflammation or inflammatory cytokine expression in an animal. Matsuomoto et al. does not teach such a method.

Claim 67 is drawn to a screening method in which a compound that inhibits TAK1/TAB1 binding is further identified as an inflammatory cytokine inhibitor. Matsuomoto et al. does not teach such a method.

In summary, since Matsuomoto et al. does not disclose all limitations of any of the independent claims (i.e., claims 41, 61, 63, and 67), it cannot anticipate any of the claims.

In view of the foregoing, applicants request that the rejection under 35 U.S.C. § 102 (b) be withdrawn.

35 U.S.C. § 102 (a)

Claims 1-9 have been rejected for anticipation in view of Ono et al. (1999). According to the Examiner, Ono *et al.* teach a method of screening for substances that inhibit the binding between TAK1 and TAB1 in various settings.

Ono et al. was published on April 29, 1999, after the priority date of the present application (October 21, 1998). A translation of the priority document accompanies this Reply. As the present claims are entitled to the October 21, 1998, priority date, the rejection for anticipation in view of Ono et al. is moot, and applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103 (a)

The Examiner has rejected claims 1-11 for obviousness over Shibuya et al. (1996) and Metzler et al. (1997) or Matsuomoto et al. (1998), in view of either Ausbel (1996), Palaparti et al. (1997), Swope et al. (1994), or Fields et al. (1989). Independent claim 1 has been cancelled



and replaced with four new independent claims, claims 41, 61, 63, and 67. To the extent that the rejection might apply to the claims as amended, applicants respectfully disagree with the rejection.

“TAK1” stands for “TGF- $\beta$ -activated kinase 1,” reflecting its originally identified function (see specification at page 1, bottom paragraph). As discussed above, Matsuomoto et al. discusses binding of TAB1 to TAK1 and activation of TAK1 by the binding, as an interaction that takes place downstream of TGF- $\beta$  in the TGF- $\beta$  signaling pathway. Similarly, Shibuya et al. discloses that TAB1 is a protein that interacts with TAK1 and acts downstream of TGF- $\beta$  in the TGF- $\beta$  signal transduction pathway. The Examiner acknowledges that Shibuya et al. does not teach screening compounds for inhibition of TAK1/TAB1 binding, but cites Metzler et al. to support the proposition that “it is common practice in the art to screen for inhibitors of binding.” (Office Action at page 7).

TGF- $\beta$  is not an inflammatory cytokine. Neither Matsuomoto et al. nor a combination of Shibuya et al. and Metzler et al. discloses a relationship between (a) binding of TAK1 to TAB1 and (b) inflammation, as required by each of the present claims. More specifically, these references do not suggest any reason to first select a compound that inhibits TAK1/TAB1 binding and then either (i) identify that compound as an inhibitor of inflammatory cytokines (claim 67), or (ii) test the compound in an assay for inhibition of inflammatory cytokine expression (claims 41 and 63) or inhibition of inflammation (claim 63). Nor do they suggest a reason to identify an inhibitor of inflammatory cytokines and then test that inhibitor for its ability to inhibit TAK1/TAB1 binding (claim 61). Thus, the primary references do not provide the motivation necessary to render the presently amended claims obvious.

None of the secondary references cited, even taken in combination, provides what is lacking in the primary references. Ausbel (1996), Palaparti et al. (1997), Swope et al. (1994), and Fields et al. (1989) were cited for their disclosures of particular assay techniques specified in dependent claims 2-11. None of these secondary references even mentions TAK1/TAB1 binding, much less links it to inflammatory processes or suggests that an inhibitor of such

binding would inhibit inflammatory cytokine expression or activity. Accordingly, no combination of the references cited by the Examiner teaches or suggests the claimed invention.

The Examiner has also rejected claim 27 under 35 USC § 103 (a) as being unpatentable over Shibuya et al. (1996) or Matsuomoto et al. (1998) in view of Shirakabe et al. (1997). According to the Examiner, since Shirakabe et al. show that TAK1 is activated by IL-1, it would have been obvious to test whether inhibitors of IL-1 also inhibit TAK1/TAB1 binding by using the methods of Shibuya et al. or Matsuomoto et al.

Applicants note that claim 27, as amended, now depends from claim 41 and so incorporates the limitations of claim 41. Claim 41 specifies a screening method that includes a step of assaying for inflammatory cytokine expression. As discussed above, Shibuya et al. and Matsuomoto et al. are both concerned with signal transduction triggered by TGF- $\beta$ , which is not a pro-inflammatory cytokine. Neither of these references suggests that an inhibitor of TGF- $\beta$  signal transduction might be found to inhibit expression of inflammatory cytokines. Thus, there would have been no reason, based on the teachings of these references regarding the role of TAB1 and/or TAK1 in TGF- $\beta$  signal transduction, to identify an inhibitor of TAK1/TAB1 binding and then test the inhibitor to determine whether it inhibits expression of an inflammatory cytokine, as required by claims 41 and 27. Shirakabe does not provide the necessary motivation or expectation of success missing from the primary references. A mere disclosure that TAK1 kinase activity can be induced by addition of IL-1 does not suggest that TAB1 binding is involved in this induction, nor that the TAK1 activity induced by IL-1 is linked to expression of inflammatory cytokines. Without this insight, there would have been no reason to carry out the screening method set forth in claims 41 and 27, as amended.

In view of the foregoing, applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103 (a).

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CONCLUSION

Applicants believe that the claims are in condition for allowance, which action is requested. It is not believed that any fees are due. Please apply any charges or credits that may be due to deposit account 06-1050, referencing attorney docket no. 14875-076001.

Respectfully submitted,

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